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Daniel J. Thompson

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KV PHARMACEUTICAL COMPANY
4080B WEDGEWAY COURT
EARTH CITY, MO 63045

EXAMINER

ARNOLD, ERNST V

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Please find below and/or attached an Office communication concerning this application or proceeding.

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/767,431
Filing Date: January 30, 2004
Appellant(s): THOMPSON ET AL.

Gary M. Nath
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/31/07 appealing from the Office action mailed 4/10/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6267985	Chen	07-2001
5266329	Riley	11-1993

Brown et al. The Journal of Reproductive Medicine 1994, 44(11), pp 933-938.

Stedman's medical dictionary 1982, 24th edition, page 334.

Garg et al. (Pharmaceutical Technology Drug Delivery 2001, pp14-24).

Droegemueller et al. (Obstet Gynecol 1984, 64(4), 530-4).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (The Journal of Reproductive Medicine 1999, 44(11), 933-938) in view of Stedman's medical dictionary 24th edition 1982, page 334.

Brown et al. disclose the use of a single dose cream formulation of 2% butoconazole nitrate for vulvovaginal candidiasis (Page 933, title, objective, results). Stedman's medical dictionary defines cream as: a semisolid emulsion of either the oil-in-water or the water-in-oil type, ordinarily intended for topical use. Thus, the cream disclosed by Brown et al. is inherently a multiphase formulation. Brown et al. disclose that of the 150 known species of *Candida*, only nine are pathogenic in humans, which are *albicans*, *glabrata*, *tropicalis*, *pseudotropicalis*,

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lusitaniae, *crusei*, *rugosa*, *parapsilosis* and *guilliermondi* (Page 934, left column). The Examiner interprets this to mean that Brown et al. define candidiasis as being caused by any of these species of *Candida*. Brown et al. disclose that the patients administered the butoconazole cream with an applicator and that the cream was spread over vaginal mucosal surfaces (Page 935, Study Drugs and their assignment). Brown et al. disclose a cure rate of 92% using single dose butoconazole cream with a kill rate over 50% in 4 days (Page 936, Table 1 and page 937, Figure 1). Brown et al. disclose that the single application regimen, efficacy and safety support the use of butoconazole for the management of vulvovaginal candidiasis (Page 938, last paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riley (US 5,266,329) in view of Brown et al. (The Journal of Reproductive Medicine 1999, 44(11), 933-

938) and Garg et al. (Pharmaceutical Technology Drug Delivery 2001, 14-24) and Droegemueller et al. (Obstet Gynecol. 1984, 64(4), 530-4) and Chen et al. (US 6,267,985).

Applicantt claims: A method for the local treatment of a vulvovaginal candidiasis condition diagnosable by a KOH smear test or other fungal speciation test, which comprises: treating said vulvovaginal candidiasis condition caused by a species of Candida selected from the group consisting of dubliniensis, tropicalis, glabrata, parapsilosis, krusei, and lusitaniae by applying to the vaginal tissue of a human a formulation comprising; about 35 to about 45% w/w sorbitol solution; about 3 to about 8% w/w propylene glycol; about 0.001 to about 1% w/w edetate disodium; about 5 to about 11% w/w mineral oil; about 0.5 to about 5% w/w polyglyceryl -3- oleate; about 0.5 to about 5% w/w glyceryl monoisostearate; about 0.001 to about 1% w/w microcrystalline wax; about 0.5 to about 2% w/w silicon dioxide; about 0.001 to about 1% w/w methylparaben; about 0.001 to about 1% w/w propylparaben; about 25 to about 45% w/w water; and about 0.5 to about 5% w/w butoconazole nitrate; and wherein the treatment is a single dose treatment.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Riley teaches systems and methods of preparation and use that release an antifungal agent such as an imidazole in a controlled manner in a vaginal cavity (Abstract). Riley teaches a composition of (in % wt/wt): 42.895 water; 39.978 sorbitol solution; 2.00 metronidazole; 0.05 EDTA disodium; 4.016 dimethicone; 4.016 mineral oil; 2.713 glyceryl isostearate; 2.713

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polyglyceryl-4 oleate; 1.013 colloidal silicon dioxide; 0.452 microcrystalline wax; 0.127 methylparaben; and 0.027 propylparaben (Column 6, lines 18-30). Note the ratio of polyglyceryl-4 oleate to glyceryl isostearate is 1:1. Riley teaches methods of treating a vaginal fungal infection wherein the active antimicrobial agent is an imidazole agent (Claims 4 and 7).

The reference of Brown et al. is discussed in detail above and that discussion is hereby incorporated by reference. Brown et al. teach the use of a single dose cream formulation of 2% butoconazole nitrate for vulvovaginal candidiasis (Page 933, title, objective, results). Brown et al. teach that of the 150 known species of *Candida*, only nine are pathogenic in humans, which are *albicans*, *glabrata*, *tropicalis*, *pseudotropicalis*, *lusitaniae*, *crusei*, *rugosa*, *parapsilosis* and *guilliermondi* (Page 934, left column). Brown et al. teach that the patients administered the butoconazole cream with an applicator (Page 935, Study Drugs and their assignment). Brown et al. teach that the butoconazole cream would adhere to the vaginal mucosal surface for a prolonged period and that of the 29% of the patients that reported vaginal leakage only 1% of the patients treated found vaginal leakage unacceptable (Page 935, left column and page 938, left column). Brown et al. teach a cure rate of 92% using single dose butoconazole cream with a kill rate over 50% in 4 days (Page 936, Table 1 and page 937, Figure 1).

Garg et al. teach pharmaceutical excipients for vaginal formulations and list propylene glycol as a humectant; preservative; solvent or cosolvent in the formulations (Page 21).

Droegemueller et al. teach that one dose of 2 % butoconazole nitrate vaginal cream results in a maximum plasma level 24 hours after dosing (Abstract).

Chen et al. teach improved delivery of therapeutic agents, including anti-fungal agents, such as butoconazole, in a composition comprising polyglyceryl 2-4 oleate (Abstract; column 29, line 19 and claim 34, for example).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Riley does not expressly teach a method with about 3 to about 8% w/w propylene glycol in the composition.

Riley does not expressly teach a method with about 0.5 to about 5% w/w butoconazole nitrite in the composition.

Riley does not expressly teach a method comprising treating a vulvovaginal candidiasis condition with a composition comprising polyglyceryl-3-oleate.

Riley does not expressly teach a method wherein the treatment provides peak plasma levels of the butoconazole nitrate at about 6 to about 48 hours after administration and retains activity for at least 4 days.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add propylene glycol, as suggested by Garg et al., butoconazole, as suggested by Brown et al. and polyglyceryl-3-oleate, as suggested by Chen et al. to the

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composition of Riley and produce the instant invention. The instantly claimed limitations of a peak plasma level of administration of butoconazole nitrate at about 6 to about 48 hours after administration is taught by Droegemueller et al. Brown et al. demonstrate the effectiveness for at least 4 days.

One of ordinary skill in the art would have been motivated to do this because Riley suggests imidazole anti-fungals for use in the composition and Brown et al. demonstrate the effectiveness of butoconazole in single dose. The addition of propylene glycol is known by one of ordinary skill the art as an excipients for vaginal formulations as taught by Garg et al. Chen et al. establish the equivalency of using polyglyceryl-2-oleate, polyglyceryl-3-oleate or polyglyceryl-4-oleate in anti-fungal drug delivery formulations. The adjustment of particular working conditions (e.g., determining the amount of propylene glycol or other ingredients to be used in the formulation and the determination of the type of species of *Candida*) is deemed merely a matter of judicious selection and routine optimization, which is well within the purview of one of ordinary skill in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

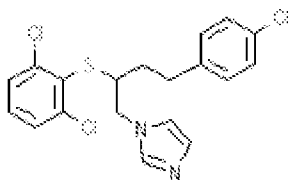
Appellant asserted that Brown et al. do not teach administration of a bioadhesive single dose treatment formulation comprising from about 0.5 to about 5.0% w/w butoconazole nitrate to a vulvovaginal fungal condition caused by a *Candida* species selected from the group consisting of *dubliniensis*, *tropicalis*, *glabrata*, *parapsilosis*, *krusei*, and *lusitaniae* and that Brown et al. only teaches that the single-dose butoconazole is effective in treating *C. albicans* alone. The Examiner still cannot agree. Brown et al. clearly discloses on page 934, lower right column that butoconazole nitrate has a “broad antifungal spectrum, consistently showing high activity against the most important eight non-*albicans* *Candida* species” and “inhibiting the growth of *C. albicans* as well as the non-*albicans* pathogenic species”. Furthermore, Brown et al. treated 101 patients with butaconazole nitrate and stated that 10-20% of the cases as non-*albicans* *Candida* species, and *C. glabrata* is the second most frequently encountered species (Page 934, left column and page 936, Table 1). Thus, Brown et al. disclose treatment of vulvovaginal fungal condition caused by at least *C. glabrata*. Simply because Brown et al. did not test for the presence of other fungal species of *Candida*, does not mean that there were not present especially in light of the fact that 10-20% of the cases are caused by non-*albicans* *Candida* species. The treatment of other *Candida* species in the method of Brown et al. is inherent in the method.

Appellant asserts: “Appellants respectfully submit that the treatments defined by the presently pending claims based on *in vivo* studies are distinguishable from the *in vitro* susceptibility noted by Lynch and Sobel.” (See cited passage in the Appeal Brief pages 18 and 19 of 42). However, the only examples in the specification are methods of preparing the samples and there are **no examples of in vivo studies** in the specification as filed. The fact remains that

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butoconazole is taught in the art to be an effective agent against a broad spectrum of *Candida* species.

Appellant asserts the secondary references provide no motivation to combine their teachings and even if one were to rely on hindsight and combine the cited references the combination would not render obvious each and every limitation of the instant invention as claimed; i.e., methods of treating nonspecified *Candida* isolates. Appellant asserts that Riley et al. teach utilizing imidazoles upon *C. albicans* and does not teach or suggest the non-*albicans* as presently claimed. The Examiner cannot agree. First, Riley teaches methods of treating a vaginal fungal infection wherein the active antimicrobial agent is an imidazole agent (Claims 4 and 7) and Brown teaches the range of species affected by butoconazole as discussed above. It is the Examiner's position that it is obvious to one of ordinary skill in the art to use butoconazole nitrate in the method of Riley because Riley directs one of ordinary skill in the art to use imidazole antifungal agents in the method (Claim 7). One of ordinary skill in the art would recognize butoconazole nitrate as an imidazole antifungal agent.



Butoconazole

Secondly, Riley et al. clearly teach delivery systems and methods to treat vaginal fungal infections thus encompassing all fungal microbes that can infect a vagina (claims 1-7). Riley et al. is

not limited to a specific microbe. Brown et al. provide the nexus teaching of the range of *Candida* species treated by butoconazole nitrate. The other secondary references are relied upon to provide teachings on the components in vaginal formulations, which would be known to one of ordinary skill in the art.

‘Appellants respectfully submit the teachings of Brown et al. as evidenced by the additional publications of J.D. Sobel, demonstrate that Brown et al., were unaware of a viable method for effectively treating the claimed non-*albicans* *Candida* species.’ The Examiner cannot agree. Brown et al. clearly teach that butoconazole has broad antifungal spectrum, consistently showing high activity against the most important eight non-*albicans* *Candida* species. The Examiner cannot be anymore clear on the subject. Brown had the knowledge that butoconazole was effective antifungal agent against *Candida* species.

Appellant states: “some investigators have questioned whether some non-*C. albicans* species cause vulvovaginal symptoms at all.”(page 25 of 42 of the Appeal brief). It appears that Appellant is attempting to establish an unpredictability in the art concerning the *in vivo* activity of the antimycotic and non-*albicans* species of *Candida* (See also pages 18, 19 of 42 of the Appeal Brief for the quoted section of Lynch). If the Examiner were to agree to such an argument then it would raise the question of enablement of Applicant’s own work because of the lack of hard *in vivo* data that would demonstrate that the instantly claimed invention actually works against the *Candida* species claimed. The facts remain that the art teaches that butoconazole as an antifungal agent against the instantly claimed *Candida* species.

‘Appellants submit that the scope and content of the prior art has been misconstrued. As evidenced by the express text of Lynch and Sobel, a need for further investigation on the role of butoconazole (and itraconazole) in experimental vaginitis was needed, especially with regard to

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vaginitis caused by non-albicans species.’ The Examiner cannot agree. Simply because Lynch and Sobel teach that more work is required does not blind one from the fact that they teach butoconazole as an effective antifungal agent against the instantly claimed Candida species. The *concept* that butoconazole is effective as an antifungal agent against the instantly claimed Candida species is established in the art.

Appellant continues: “Additionally, as evidenced by the abstracts submitted herewith, Appellants note Sobel, even after Brown et al. was published, did not appear to obtain the presently claimed subject matter. Accordingly, Appellants submit that a person of ordinary skill in the art could only arrive at the presently pending subject matter by way of impermissible hindsight, i.e., construing the scope and contents of the prior art in view of the teachings of the present application.” The Examiner cannot agree. From the teachings in the art as described above, one of ordinary skill in the art would have a reasonable expectation of success of treating non-albicans Candida infections with the antifungal agent butoconazole with the predictable outcome of killing the non-albicans Candida species because the art teaches that butoconazole is effective at killing the non-albicans Candida species.

In conclusion, Appellant continues to argue the references and has not provided a showing of unexpected results. Appellant’s arguments are not persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner’s answer.

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For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

Conferees:

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

/Ernst V Arnold/
Examiner, Art Unit 1616

Ernst Arnold